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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,288	01/25/2002	Christian P. Larsen	D0136NP/30436.58USU1	1849

23914 7590 11/29/2005

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,288	LARSEN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-13,17,30,33-37,44-52 and 54-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-13,17,30,33-37,44-52 and 54-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 9/11/05, has been entered.
Claims 24-26, 28-29, 31-32 and 53 have been canceled.
Claims 7-8, 14-16, 18-23, 27 and 38-43 have been canceled previously.

Claims 1, 3, 9, 17, 30, 34, 35, 50, 52, 55 and 56 have been amended.

Claims 57-63 have been added.

Claims 1-6, 9-13, 17, 30, 33-37, 44-52 and 54-63 are pending.

2. Applicant's election of the following species:
the alkylating agent is busulfan;
the first ligand is a soluble CTLA4;
the second ligand is anti-CD40 antibody; and
the targeted condition is solid organ or tissue/cellular transplant
with traverse has been acknowledged.

Given amending the claims to provide the alkylating agent / busulfan after the administration of bone marrow derived stem cells,
the search has been extended to another alkylating agent (i.e. cyclophosphamide) in view of the enablement issues under 35 USC 112, first paragraph, indicated herein for "administering the elected alkylating agent busulfan after the administration of bone marrow cells / stem cells" indicated below and in the interest of compact prosecution.

Claims 1-6, 9-13, 17, 28-37 and 44-52 and 54-56 are being examined to the extent that they read on the elected species (e.g. busulfan as well as cyclophosphamide, the first ligand is a soluble CTLA4, the second ligand is anti-CD40 antibody and the targeted condition is solid organ or tissue/cellular transplant) for examination purposes in the instant application.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed in applicant's amendment, filed 9/1/05.
The rejections of record can be found in the previous Office Action.

4. Upon reconsideration of applicant's amendment, including amending the instant specification to include the proper sequence identifiers, filed 9/11/05;
it appears that the instant application is compliance with the sequence rules.

5. The filing date of the instant claims is deemed to be the filing date of priority application USSN 60/303,142, filed 7/5/01.

In contrast to applicant's reliance,
the disclosure of experimental observations concerning the ability of a single dose of busulfan prior to the transplantation (i.e. intravenous infusion) of T cell-depleted bone marrow cells (e.g. comprising hemopoietic stem cells) in priority USSN 60/264,528, filed 1/26/05;
does not provide sufficient written description for
(a) "administering TDBM before, during and/or after a solid organ or tissue/cellular transplant";
(b) "subsequently administering an alkylating agent (including busulfan)"; or
(c) "administering an immunosuppressive composition before, during and/or after a solid organ or tissue/cellular transplant", as currently claimed.

These instant claims encompass limitations that represent a departure from the priority USSN 60/264,528, filed1/26/05. Applicant's reliance on a limited disclosure and possibly a single or limited species (e.g. busulfan) under certain defined conditions do/does not provide sufficient direction and guidance to the written description of the currently claimed "limitations". It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Therefore, as indicated previously, priority application USSN 60/264,528, filed 1/26/01 does not appear to support the instant claims encompassing methods of inhibiting rejection of a solid organ or tissue/cellular transplant by administering an alkylating agent (e.g. bulsufan) and subsequently administering T cell depleted bone marrow cells before, during or after as the transplant, as well as administering CD28 / CD80 / CD86 / CD154 / CD40 inhibitors.

Therefore, the filing date of the instant claims is still deemed to be the filing date of priority application USSN 60/303,142, filed 7/5/01.

If applicant desires priority prior to 7/5/01; applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earliest priority application asserted.
Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

6. Applicant's amendments to the Title and the Abstract to read on the claimed invention is acknowledged.

7. New Grounds of Rejection: New Matter

Claims 57, 59 and 63 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed:

The dosages set forth in claims 57, 59 and 63 as they read on any alkylating agent rather than the specific alkylating agent busulfan.

Applicant's amendment, filed 9/11/05, directs support to pages 27, 30, 47 and Example 1 of the instant specification.

However, these sections appear to only provide written support for the claimed dosages with respect to the specific alkylating agent busulfan and not generically on any alkylating agent.

"For example, bulsulfan may be administered in an amount between 0.1 mg to 20 mg/kg weight of the subject, e.g. 4 mg/kg, 8-16 mg/kg, 4-16 mg/kg." See page 27, lines 24-25 of the instant specification.

Therefore, the instant claims encompass limitations that represent a departure from the instant disclosure as filed. Applicant's reliance on a limited disclosure and possibly a single or limited species (e.g. busulfan) under certain defined dosages does not provide sufficient direction and guidance to the written description of the currently claimed "dosage limitations" as they read on "any alkylating agent". It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The specification as filed does not provide sufficient written description, nor provide sufficient blazemarks for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action
Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.
See MPEP 714.02 and 2163.06

8. New Grounds of Rejection: Enablement.

Claims 1-6, 9-13, 17, 30, 33, 44-52, 54 and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs can be species- and model-dependent, it is not clear that reliance on the experimental and clinical experience with alkylating agents, particularly the elected species busulfan, accurately reflects the relative ability of administering subsequent to bone marrow transplantation or hemopoietic stem cell transplantation in the absence of a second dose of said cells encompassed by the claimed therapeutic strategy.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The use of alkylating therapy including busulfan can destroy the bone marrow microenvironment as well as hemopoietic stem cells in therapeutic regimens for facilitating engraftment of bone marrow cells (e.g. see US 20030007968 A1, paragraph [0009]).

Given the claimed recitation of administering alkylating agents such as bulsufan subsequent to bone marrow cells, it appears that that claimed methods are drawn to administering alkylating agents such as the elected species busulfan would destroy the hemopoietic microenvironment as well as the hemopoietic stem cells themselves.

Therefore, the skilled artisan could not predict the efficacy of administering bulfulsan subsequent to bone marrow transplantation would inhibit transplant rejection, given that bulsulfan would destroy or damage both the hemopoieitc microenvironment and bone marrow cells / hemopoietic stem cells themselves.

While certain alkylating agents (e.g. cyclophosphamide) have been used as immunosuppressives in transplantation regimens, including prior to, during and after transplantation,
certain alkylating agents such as the elected species bulsulfan that destroy both the hemopoietic microenvironment and hemopoietic stem cells appear to be inappropriate for the claimed method of inhibiting transplant rejection.

The specification does not adequately teach how to effectively treat inhibit transplant rejection with administering any "alkylating agent", particularly those alkylating agents such as the elected species busulfan which destroys or damages the hemopoietic microenvironment and hemopoietic stem cells subsequent to admininstering the bone marrow cells / hemopoietic stem cells.

Also, it is noted that the instant examples appear to rely upon the administration of busulfan prior to and not after bone marrow / hemopoietic stem cell transplantation in providing the appropriate conditions and space for bone marrow / hemopoietic stem cell transplantation.

In those Examples 3 and 4 disclosed on pages of the instant specification,
where busulfan is administered subsequent to bone marrow cells, a second administration of bone marrow cells are administered to provide for the long term effect of promoting graft survival and that this second administration of bone marrow cells occurs in timing close to the transplant itself.

The instant claims do not provide for a dosing regimen of the various elements that would lead the ordinary artisan to predict that administering busulfan shortly after bone marrow cells would inhibit graft rejection as broadly encompassed by the claimed invention.

Without sufficient guidance, administering any alkylating agent, particularly the elected busulfan species, after bone marrow / hemopoietic stem cell transplantation would appear to damage if not destroy the very bone marrow cells / hemopoietic stem cells previously transplanted and still provide or maintain the purpose and biological activities of the transplanted T cell depleted bone marrow cells is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Again, it is noted that certain alkylating agents such as cyclophosphamide have been practiced in transplantation regimens as immunosuppressive agents before, during and after transplantation.

Applicant is invited to provide objective evidence for the enablement of the scope of alkylating agents encompassed by the claimed methods.

Applicant is invited to consider amending the claims to provide for a therapeutic dosing of the various agents that would lead to the inhibit graft rejection, as broadly encompassed by the claimed invention and as it reads on the elected species busulfan in particular.

9. Claims 47-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific mutant CTLA4 molecules such as the L104EA29YIg molecule disclosed in the specification as filed or claimed (e.g. see Example 8 on pages 67-83 of the instant specification), does not reasonably provide enablement for any "CTLA4 mutant molecule" to be employed as an immunosuppressive agent in the instant claimed methods.
The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 9/11/05, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant acknowledges that CTLA4 mutant molecule means wildtype CTLA4 as shown in Figure 19 or any portion or derivative thereof, that has a mutation or multiple mutations and submits Examples of six CTLA4 mutant molecules are provided.

Applicant relies upon disclosing a number of different assays for the identification of CTLA4 mutant molecules as claimed.

However, such assays without more precise guidelines amount to little more that a starting point, a direction for further research. The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention for any mutant CTLA4 molecule including any mutation or mutations as well as any derivative of CTLA4 as broadly encompassed by the claimed invention. At most, its description will enable a person of skill in the art to attempt to discover how to practice the claimed invention, which is not enough.

The following of record is provided for applicant's convenience.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies any "CTLA4 mutant molecule" that inhibits graft rejection encompassed by the claimed methods. "CTLA4 mutant molecule" may have some notion of the source of the "first ligand that interferes with binding of CD28 to either CD80 or CD86", however, claiming biochemical molecules by a particular name and a modification of said molecule (e.g. "CTLA4 mutant molecule") by applicant fails to distinctly claim what that "CTLA4 mutant molecule" is and what it is made up of or how it differs from native CTLA4. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "CTLA4 mutant molecule".

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus of "CTLA4 mutant molecules". The instant invention encompasses any "CTLA4 mutant molecule", yet the instant specification does not provide sufficient guidance and direction as to the selection of particular sequences essential for the unrecited (claim 47) and recited function (see claim 48), which interferes with binding of CD28 to either CD80 or CD86 in the inhibition of graft rejection.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "CTLA4 mutant molecules" other than the CTLA4 mutant molecules disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of ligand and receptors encompassed by the claimed invention.

Attwood (Science 290: 471–473, 2000) notes in the Introductory paragraphs that it is presumptuous to make functional assignments merely on the basis of some degrees of similarity between sequences (and it is not always clear what we mean by "function"); very few structures are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently tellus functions").

Skolnick et al. (Trends in Biotechnology 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

This requirement is emphasized in the instant example since, as summarized in Figures 2 and 3 of Coyle et al. (Nature Immunology 2: 203-209, 2001) the B7-like family members have distinct expression patterns and distinct functions.

Metzler et al. (Nature Structural Biology 4: 527- 531, 1997) describe various CTLA4 mutants and their varying effects on CD80 and CD86 binding (see entire document, including Table 2 on page 530). Here, there does not appear sufficient predictability as to those mutations that result in a particular function, as the mutations had multiple effects on said CD80 and CD86 binding, including little or no effects.

Thus, the experimentation left to those skilled in the art to determine the function of the scope of "CTLA4 mutant molecules" that interfere with binding of CD28 to either CD80 and CD86 and inhibit graft rejection encompassed by the claimed invention is unnecessarily and improperly extensive and undue.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus of "CTLA4 mutant molecules". It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of receptors and ligands.

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use "CTLA4 mutant molecules" other than those specific "CTLA mutant molecules" which interfere with the binding of CD28 to either CD80 or CD86 as disclosed in the specification as filed (or as recited in claims 49-50) as the first ligand in the claimed methods to inhibit graft rejection.

Applicant is invited to limit the claims to those "CTLA4 mutant molecules" with the appropriate inhibitory properties disclosed in the specification as filed as the first ligand in the claimed methods.

10. Given applicant's amended claims deleting the recitation, the previous rejection under 35 U.S.C. 112, first paragraph, enablement for the deposit of biological materials has been withdrawn.

Applicant's statements concerning the deposit under the Budapest Treaty and the appropriate assurances concerning of L104EA29YIg are acknowledged, however, the claims no longer recite "L104EA29YIg".

11. Claim 30 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 30 is indefinite is providing "busulfan prior to solid organ or tissue/cellular transplant, given applicant's amended claims to recite "(b) subsequently administering an alkylating agent ... ". Further, it is noted that applicant's argues that the amended claims have obviated the prior art teachings given the administration of busulfan after transplantation.

The dependent claims conflict with the recitation of the claims that they depend upon and therefore are ambiguous and do not particularly point out and distinctly claim the invention.

B) Given applicant's amended claims deleting the recitation of "L104EA29YIg", the previous rejection with respect to claims 50 and 56 with respect to the recitation of "L104EA29YIg" has been withdrawn.

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

12. Given applicant's amended claims, filed 9/11/05; which now recited "administering busulfan / alkylating agents subsequent to bone marrow cell transplantation, certain dosages of busulfan / alkylating agents and a second administration of bone marrow cells,

the previous rejection under 35 U.S.C. 102(e) as being anticipated by Sykes (U.S. Patent No. 6,514,513) has been withdrawn.

13. Claims 1-6, 9-13, 17, 30, 33-37, 44-52 and 54-63 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513) in view of art known practice and modes of administration of alkylating agents

such as bulsulfan at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994)

or cyclophosphamide for the reasons of record and in further view of The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide) and Shichi et al. (U.S. Patent No. 4,843,092).

As pointed out above, given amending the claims to provide the alkylating agent subsequent to the administration of bone marrow derived stem cells,

the search has been extended to another alkylating agent in view of the enablement issues under 35 USC 112, first paragraph, indicated above for "administering the elected alkylating agent busulfan after the administration of bone marrow cells" indicated herein and in the interest of compact prosecution.

As indicated above, the prior art does not appear to provide a clear teaching (or motivation) to administer busulfan subsequent to bone marrow transplantation,

given the ability of busulfan to damage or destroy the hemopoietic microenvironment and hemopoietic stem cells.

Applicant's arguments, filed 9/11/05,have been fully considered but are not found convincing with respect to those claims that do not require that busulfan to be administered subsequently to the administration of bone marrow cells (or hemopoietic stem cells).

For example, independent claim 34 does not require that busulfan be administered subsequent to bone marrow cells and that busulfan is an immunosuppressive agent, but not necessarily the one required for step (d) (e.g. "an immunosuppressive composition").

Also, in contrast to applicant's arguments, Sykes is not limited to the use of only irradiation in the methods described, as indicated herein and of record.

Further in view of applicant's amended and newly added claims, Sykes teaches one or more post-graft implantation administrations of donor stem cells (e.g. see column 7, paragraphs 1 – 2; column 9, paragraph 11 – column 10, paragraph 3).

In addition, Sykes teaches the known use of immunosuppressive agents prior to, during and after bone marrow or stem cell transplantation to promote long term graft survival and immunological tolerance (e.g. see column 7, paragraph 6 – column 8, paragraph 1; column 11, paragraphs 3-4; column 15, paragraph 2; column 16, paragraphs 2 and 5; and column 17, paragraph 3).

While applicant argues that Sykes does not expressly disclose that administering busulfan in amounts that facilitates mixed hemopoietic chimerism, one cannot separate a product from its properties. Further, in this case, applicant acknowledges the use of busulfan to create hemopoietic space, therefore the effective amount of busulfan taught by the prior art does inherently facilitate hemopoietic chimerism.

With respect to the use an alkylating agent such as cyclophosphamide as an immunosuppressive agent, which can be administered subsequent to the administering T cell depleted bone marrow cells to a subject in a transplantation regimen, the following is noted.

The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 describes the known use of immunosuppressive drugs such as the aklylating agent cyclophosphamide in after transplantation and during rejection crises as well as maintenance regimens with relatively small doses of immunosuppressants (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide).

Shichi et al. (U.S. Patent No. 4,843,092) similarly teach the known use of immunosuppressive agents such as the alkylating agent cyclophosphamide as agents for suppressing rejection which may occur after transplantation of human organs (see column 1, second paragraph of Background Art).

Therefore, one of ordinary skill in the art would have administered the alkylating agent cyclophosphamide at various times prior to, during and subsequent to transplanting cells and tissues in order to provide the appropriate immunosuppressive environment to promote long term acceptance of transplants / grafts. It is clear that cyclophosphamide has been used for decades by the ordinary artisan in transplantation regimens.

Also, as indicated previously, the claimed timing and dosages of alkylating agents including busulfan or cyclophosphamide in the claimed therapeutic methods to inhibit rejection of transplant was obvious to one of ordinary skill in the art at the time the invention was made, as these limitations appear to be consistent with those employed in the prior art and with providing efficacy and bioavailability, while minimizing drug associated toxicities.

The following of record is provided for applicant's convenience.

Sykes teach methods inducing specific nonresponsiveness or tolerance to various antigens by inducing hemopoietic chimerism, including transplant antigens by administering

T cell depleted bone marrow cells / stem cells (e.g. see columns 6-7; column 8, lines 53-55; columns 9-11, column 15, paragraph 1) (note: stem cells read on T cell depleted bone marrow cells);

hemopoietic space agents, including busulfan (e.g. see column 8, paragraph 1);,

CD40L-CD40 inhibitors, including antibodies that bind CD40 and

CD28-B7 inhibitors, including CTLA4Ig (e.g. see column 8, line 65 - column, line 36; column 12)

as it relates to tissue and organ transplantation (see entire document, including Summary of the Invention; Detailed Description; Claims).

In addition, Sykes describes numerous modes of administration of providing the above-mentioned elements of therapeutic regimen in combination before, concurrently and subsequent to transplantation (see Summary of the Invention and Detailed Description).

Administering bone marrow stem cells, including repeated administration of said cells prior to, during and after the transplant are described (see Summary of the Invention, including column 2, line 60 – column 3, line 49; and Detailed Description, including column 6, line 38 – column 7, line 46; columns 9 – 10)

Sykes differs from the claimed methods by not disclosing the particular timing of busulfan in the claimed therapeutic methods to promote graft survival (e.g. see claims 30-32). Claims 1-2 and 9-10 encompass the particular timing of busulfan administration encompassed by claims 30-32.

As acknowledged on pages 26-27 of the instant specification including the citation of Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148; see entire documents); modes of administering busulfan were known at the time the invention was made. Therefore, one of ordinary skill in the art would have been motivated to administer busulfan at various times, including the claimed timing (e.g. see claims 30-32) to create hemopoietic space for T cell depleted bone marrow / stem cells as well as to optimize bioavailability.

Slattery et al. teach that busulfan is an alkylating agents commonly used to ablate marrow before hemopoietic stem cell transplantation and the importance of analytical and pharmacokinetic aspects of therapeutic monitoring (see entire document, including the Summary on page 543). It is noted that the patients revied bulsulfant doses every 6 hours over a period of 4 days (see Busulfan Concentration and Outcome of Transplantation).

Similarly Hassan et al. teach the known use of busulfan in myeloablative therapy in bone marrow transplantation and the importance of drug monitoring and individual dose adjustment in providing for busulfan bioavailability while reducing / avoiding drug-related toxicities (See entire document, including the Abstract).

Therefore, the claimed timing of busulfan in the claimed therapeutic methods to inhibit rejection of transplant was obvious to one of ordinary skill in the art at the time the invention was made, as these limitations appear to be consistent with those employed in the prior art and with providing busulfan efficacy and bioavailability, while minimizing drug associated toxicities.

Given the general applicability and desirability of the modes of inducing immunological nonresponsiveness to a variety of antigens, including a wide variety of cells, tissues and organs of interest, one of ordinary skill in the art would have been motivated to include the well known transplantation of skin grafts to the transplantation regimens taught by Sykes.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 1, 9 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513)
in view of art known practice and modes of administration of alkylating agents
such as bulsulfan at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994)
or cyclophosphamide for the reasons of record and in further view of The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide) and Shichi et al. (U.S. Patent No. 4,843,092).

and in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449, Exhibit 225)
essentially for the reasons of record.

The teachings are set forth above.

As indicated previously, Sykes differs from the claimed methods by not disclosing "skin" per se as the tissue of organ of interest for transplantation. Claims 1 and 9 encompass skin grafts as the tissue / organ transplant of the claimed methods

Larsen et al. teach modes of inhibiting immune responses, including rejection of various tissues and organs including skin (e.g. see column 2; column 6, paragraph 4) by blocking CD40:CD40L and CTLA4:CD28:B7 pathways in order to induce immunological unresponsiveness in the transplant recipient (see entire document, including Background of the Invention, Summary of the Invention, Detailed Description and Claims).

Given the general applicability and desirability of the modes of inducing immunological nonresponsiveness to a variety of antigens, including a wide variety of cells, tissues and organs of interest, as taught by Sykes and Larsen et al.,one of ordinary skill in the art would have been motivated to include the well known transplantation of skin grafts to the transplantation regimens taught by Sykes, given the evidence by Larsen et al. that skin is among a list of known tissues that were routinely transplanted at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments and the examiner's rebuttal are essentially the same as above with respect to the rejection of record as well as with respect to applicant's newly amended claims.

Applicant's arguments have not been found persuasive.

15. Claims 1, 5, 9, 11, 12, 34-36, 44-52, 54, and 56, 60-61 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513)

in view of art known practice and modes of administration of alkylating agents

such as bulsulfan at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994)

or cyclophosphamide for the reasons of record and in further view of The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide) and Shichi et al. (U.S. Patent No. 4,843,092).

and in view of Peach et al. (US 20020182211) essentially for the reasons of record.

The teachings are set forth above.

Sykes differs from the claimed methods by not disclosing the particular mutant CTLA4 mutant molecules, including L104EA29Yig CTLA4 recited in the instant claims as the inhibitory CTLA4 of the claimed invention.

Peach et al. teach soluble CTLA4 mutant molecules, including the specific L104EA29YIg, which have greater avidity than CTLA4 and can bind either of CD80, CD86 or both (e.g., see Summary of the Invention) in immunomodulating regimens for the treatment or prevention of acute or chronic graft rejection, including in combination therapy (e.g. see paragraphs [0079] – [0084] on pages 8-9). The claimed extracellular domains as well as the claimed sequences (e.g. claims 44-52 and 56) are intrinsic properties of the referenced CTLA4 mutant molecules, including the specific L104EA29YIg taught by Peach et al.

Given the greater avidity soluble CTLA4 mutant molecules, including the specific L104EA29YIg, which can bind either of CD80, CD86 or both, one of ordinary skill in the art would have been motivated to substitute said soluble CTLA4 mutant molecules taught by Peach et al. in the referenced transplantation regimens taught by Sykes, in an effort to increase the efficacy of CTLA4 molecules to inhibit the desired CTLA4-mediated responses in promoting long term graft survival at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments and the examiner's rebuttal are essentially the same as above with respect to the rejection of record as well as with respect to applicant's newly amended claims.

Applicant's arguments have not been found persuasive.

16. Applicant's arguments concerning the unexpected advantages are acknowledged.

However, it appears that Examples 2 and 3 on pages 49-53 of the instant specification that applicant relies upon for unobviousness appears to administer two separate dosages of bone marrow cells in particular dosages and in a particular timing scheme, wherein the second dosage of bone marrow cells follows shortly after the administration of busulfan.

Applicant's Examples requires a particular dosing regimen and that bone marrow cells need to be administered subsequent to busulfan administration.

Applicant argues limitations not claimed.

Therefore, the rejections are maintained for the reasons of record and that set forth herein.

Also, as pointed out above, the administration of alkylating agents such as cyclophosphamide prior to, during and post transplantation was considered routine and obvious in transplantation regimens at the time the invention was made.

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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November 23, 2005